Article

Parasympathetic Nerve Function Status in Postmenopausal Women

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Background: In postmenopausal women, the risk of cardiovascular diseases gradually increases and alterations in autonomic nerve functions commonly affect cardiac vagal control. **Objective:** To observe some aspects of parasympathetic nerve function status in apparently healthy post menopausal women. **Method:** This cross sectional study was carried out in the Department of Physiology Bangabandhu Sheikh Mujib Medical University. In this study, 30 postmenopausal women with age 45 to 60 years were included in group B (study group) and 30 premenopausal women aged 20 to 30 years were taken in group A (control group). They were further divided into group A1(menstrual),A2(follicular), A3(luteal) according to phases of menstrual cycle during which they were studied. Serum estrogen and progesterone levels were measured in postmenopausal women and also during follicular and luteal phases in premenopausal women and were estimated by MEIA technique. To assess parasympathetic nerve function status, three noninvasive cardiovascular reflex tests such as heart rate response to valsalva maneuver, heart rate response to deep breathing and heart rate response to standing were performed in all the subjects. Data were collected by recording ECG in resting conditions. For statistical analysis, unpaired t test and multiple regression analysis was used. **Results:** In postmenopausal women, serum estrogen and progesterone levels were significantly ($p<0.001$) lower compared to those of follicular and luteal phases of premenopausal women except progesterone level during follicular phase which was though lower but not statistically significant. Heart rate response to valsalva maneuver were almost similar in all the groups.Heart rate response to deep breathing and heart rate response to standing were significantly lower in group B than those of group A1, A2 and A3 respectively. On regression analysis parasympathetic nerve function in post postmenopausal women showed significant association with estrogen level. **Conclusion:** From this study it may be concluded that parasympathetic nerve function was lower in postmenopausal women, which may be related to decreased level of estrogen

Key Words: Postmenopausal women, Parasympathetic nerve function, Cardiovascular reflex test.

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Introduction

Menopause is a normal aging phenomenon in women[1], when ovaries become non-responsive to pituitary gonadotropic hormones leading to a gradual decline in the production of ovarian hormones[2]. Estrogen deficiency have a remarkable effect on skeletal, urogenital and also on cardiovascular system in postmenopausal women[3]. The reported level of estradiol is 5-25 pg/ml, estrone 20-70 pg/ml and progesterone 0.17 ng/ml in postmenopausal women[2].

The risk of cardiovascular diseases gradually increases in postmenopausal women,which may be due to lower level of estrogen[4]. Alterations in autonomic nerve functions may occur in

menopausal women and it commonly affects cardiac vagal control and usually associated with sympathetic hyperactivity[5]. Various research evidences suggest that cardiovascular autonomic balance is related to baroreceptor sensitivity and heart rate variability [3]. Overiectomy suppresses baroreflex sensitivity and HRV [6].It has also been demonstrated that hormone replacement therapy in postmenopausal women increases baroreflex sensitivity and HRV[7] ,which in turn improves parasympathetic control of the heart [4,8]. However, some other group of investigators found no improvement of cardiac autonomic nerve dysfunctions following estrogen administration[9].

A significant number of post menopausal women are part of the elderly female population in our country. They often suffer from various menopause related complications including autonomic nerve dysfunction.Therefore, the present study was conducted to observe the parasympathetic nerve function status in healthy postmenopausal women to identify any deviation from normal autonomic nerve function activity in this group of women.

Methods

This cross sectional study was carried out in the department of Physiology, BSMMU from January to December 2007 on 30 apparently healthy postmenopausal women aged 45 to 60 years (Group B). Again, 30 healthy premenopausal women with age ranged from 20 to 30 years were taken as control(Group A). Before recruitment, the objectives of the study were explained to the subjects and their voluntary participation were encouraged. All procedures for ethical clearance were followed and a written informed consent was taken from each subject. The protocol of the study was approved by the ethical committee of the department of Physiology BSMMU. Control group was studied during menstrual(A1), follicular(GroupA2) and luteal (Group A3) phases of menstrual cycle. Post menopausal women were studied once. Detailed family history, medical history, menstrual history and menopausal history were taken. Random Blood Sugar level and Creatinine clearance were measured to exclude diabetes mellitus and renal failure. Resting heart rate and blood pressure of all subjects were also measured. Serum estrogen and progesterone levels of all subjects were estimated by MEIA method. In addition, parasympathetic nerve function was evaluated in all the groups by the conventional method performing 3 cardiovascular reflex tests namely heart rate response to valsalva maneuver, heart rate response to deep breathing and heart rate response to standing.

Data were analyzed by unpaired t test. Multiple regression analysis was done to observe the association of age, BMI, progesterone and serum estrogen levels with the parasympathetic nerve function variables.

Results

General characteristics of all the subjects are shown in Table I. In this study, parasympathetic nerve function variables in post menopausal women were compared with those during three phases of menstrual cycle in premenopausal women. Mean serum estrogen level was significantly ($p<0.001$) lower in postmenopausal women than those of during follicular and luteal phases in premenopausal women (Table II). Serum Progesterone level was significantly ($P<0.001$) lower in postmenopausal women than its value during luteal phase. Again, these values were lower than the value observed during follicular phase but the difference was not statistically ($P>0.05$) significant (Table II).

The results of parasympathetic nerve function tests are shown in Table III. Group B had almost similar value of valsalva ratio to those of group A1, A2 and A3. However, Heart rate response to deep breathing and heart rate response to standing were significantly lower in group B than those of group A1, A2 and A3. All these parasympathetic nerve function parameters were

compared among the different phases of menstrual cycle in premenopausal women and no statistically significant differences were observed among the groups.

Regression analysis showed significant association of serum estrogen with valsalva ratio ($P<0.01$), heart rate response to deep breathing ($p<0.05$) and heart rate response to standing ($p<0.05$) (Table IV).

Table I: Age, BMI and waist hip circumference ratio in different groups (n=60)

Variables	Group A (n=30)	Group B (n=30)
Age (years)	24.30±3.88	50.53±3.02***
BMI (kg/m^2)	20.80±1.40	22.18±3.08*
W:H	0.79±0.04	0.83±0.05

Data expressed as mean±SD
Group A= Premenopausal women
Group B= Postmenopausal women
***= p<0.001, *= p<0.05

Table II: Serum estrogen and progesterone levels in different groups(n= 60)

Groups	Sub groups	Estrogen (pg/ml)	Progesterone (ng/ml)
A (n=30)	A2	155.36±69.03	0.85±0.60
	A3	138.20±56.73	1.12±3.92
B (n=30)		21.93±10.46	0.20±0.15
Statistical analysis		p values	
A2 vs A3		0.204 ns	0.000***
B vs A2		0.000***	0.275 ns
B vs A3		0.000***	0.000***

Data expressed as mean±SD
A= Premenopause (control)
A2= follicular phase
A3 = luteal phase
B= Postmenopause (study)
***= significant at the p<0.001, n = Number of subjects, ns = p > 0.05

Table III: Parasympathetic nerve function variables in different groups (n=60)

Groups	Subgroups	Heart rate response to		
		Valsalva maneuver (valsalva ratio)	Deep breathing (beats/min)	Standing (30^{th}: 15^{th})
A (n=30)	A1	1.36±0.18	25.14±7.84	1.19±0.21
	A2	1.41±0.18	26.79±7.09	1.20±0.26
B (n=30)	A3	1.40±0.21	26.82±7.41	1.17±0.11
		1.44±0.32	12.62±3.83	1.07±0.08
Statistical analysis Groups		P values		
B vs A1	0.204 ns	0.000***	0.011*	
B vs A2	0.628 ns	0.000***	0.009**	
B vs A3	0.535 ns	0.000***	0.038*	
A1 vs A2	0.430 ns	0.346 ns	0.922 ns	
A1 vs A3	0.513 ns	0.338 ns	0.631 ns	
A2 vs A3	0.892 ns	0.987 ns	0.564 ns	

Data expressed as mean±SD
A= Premenopause (control)
A1= menstrual phase
A2= follicular phase
A3 = luteal phase
B= Postmenopause (study)
***= p<0.001, **= p<0.01 *= p<0.05, ns= non significant, n= total number of subjects

Table IV: Linear regression analysis evaluating the association between parasympathetic function parameters with serum estrogen, progesterone, age and BMI in postmenopausal subjects(n=30)

Independent variables	Dependant variables					
	Heart rate response to valsalva maneuver		Heart rate response to deep breathing		Heart rate response to standing	
	β coefficient	p value	β coefficient	p value	β coefficient	p value
Serum estrogen	0.542	0.002**	0.479	0.01*	0.406	0.029*
Serum progesterone	0.166	0.312^{ns}	-0.254	0.154^{ns}	0.117	0.511^{ns}
Age	-0.232	0.163^{ns}	-0.141	0.425^{ns}	-0.163	0.361^{ns}
BMI	0.078	0.629^{ns}	-0.073	0.674^{ns}	0.231	0.194^{ns}

**=p<0.01
*= p<0.05
ns= p>0.05

Discussion

In this study, serum estrogen level in postmenopausal women was significantly lower than any of its values during any phase of ovarian cycle in premenopausal women. Fadel et al. (2004) also observed similar findings in postmenopausal women in comparison to that of follicular phase of premenopausal women.

Again, significantly lower value of mean serum progesterone level was found in post menopausal women compared to luteal phase but it was not statistically significant compared to follicular phase. No data was available to compare this finding.

The parasympathetic nerve function parameters i.e heart rate (HR) response to valsalva maneuver, HR response to deep breathing, HR response to standing in post menopausal women have shown variation. In this study, data did not show any significant difference in valsalva ratio, but significantly lower HR response to deep breathing and heart rate response to standing were observed in postmenopausal women compared to those during three phases of menstrual cycle in premenopausal women. Virtanen et al (1999) observed lower values of HR response to deep breathing in post-menopausal women but they did not compare these parameters with premenopausal women

On the other hand, in premenopausal women, valsalva ratios, HR response to deep breathing and HR response to standing (30^{th}:15^{th} ratios) were almost similar during three phases of menstrual cycle. Fuenmayer et al. have demonstrated significantly higher value of valsalva ratio during luteal phase compared to menstrual phase[13]. Mehta and Chakrabarty[14] made similar observations regarding HR response to standing[14].

Again, Rosano et al. (1997) and Neves et al. (2007) reported decreased parasympathetic nerve function in postmenopausal women. However, they used power spectral analysis of HRV for evaluation of parasympathetic nerve function[4,15]. In addition to these observations, significant association of all parasympathetic nerve function parameters with estrogen level has been revealed in postmenopausal women.

In the present study, significantly lower HR response to deep breathing and 30^{th}:15^{th} ratios

are suggestive of decreased baroreceptor reflex activity and vagal tone, which may be due to decreased level of estrogen in this group of women [12] .However, the role of estrogen on autonomic nerve function has not yet been clearly indicated. It has been suggested that estrogen may have some effects on central baroreflex mechanism. It facilitates the glutamatergic neurotransmission in the nucleus tractus soliterius[10]. It also increases baroreflex sensitivity as well as vagal tone[11]. Therefore, decrease in baroreflex sensitivity, HRV, parasympathetic activity may be the consequences of estrogen deficiency in postmenopausal women[12].

In a study on hormone replacement therapy on post menopausal women, Rosano et al(1997) found lower parasympathetic nerve function and sympathetic hyperactivity in postmenopausal women which was shown improved with estrogen replacement therapy[4]. Decreased level of estrogen in postmenopausal women may cause alterations of parasympathetic nerve function. However, the exact mechanisms involved for this impairment cannot be elucidated from this study. Study after supplementation of estrogen in this group of women may give more conclusive findings.

Conclusion

From the features of the present study it may be concluded that the parasympathetic cardiac autonomic nerve function may be lower after menopause with associated estrogen deficiency.

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